Natural bond orbital analysis of hyperconjugative stabilization effects in the transition states of cyclohexanone reduction with $LiAlH_4$

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Natural bond orbital (NBO) analysis of the transition states of cyclohexanone reduction with $LiAlH_4$ located at the B3LYP/6-31+G(d) level along the intrinsic reaction coordinate (IRC) strongly indicate that the antiperiplanar effect involving the incipient bond may not be important as a controlling factor of π-facial selection in carbonyl reduction.

Since Cieplak[1] proposed the theory of π-facial stereoselectivity in 1981, the direction of the antiperiplanar hyperconjugative stabilization effects (hereafter abbreviated as 'the AP effect') in the transition states of nucleophilic carbonyl addition have been the subject of intense investigation in both theoretical and experimental organic chemistry.[2] While the Felkin–Anh model[3] postulated the AP effect between the filled electron-rich incipient bond and the vacant vicinal antiperiplanar bonds, Cieplak predicted the opposite electronic property in common organic reactions, proposing exactly the reverse AP effect.[1] Herein we report the first transition state of the reduction of cyclohexanone with $LiAlH_4$ together with the natural bond orbital (NBO)[4] analysis of the AP effects along the intrinsic reaction coordinate towards the transition state.

The structures of the axial (*ax*-TS) and equatorial (*eq*-TS) transition states of cyclohexanone reduction with $LiAlH_4$ optimized at the B3LYP/6-31+G(d) level are shown in Fig. 1. The zero point vibrational energy corrected relative electronic energy was 1.36 kcal mol^{-1}, slightly favoring the *ax*-TS in agreement with experiment. Each transition state had a single imaginary vibrational frequency corresponding to the stretching vibration of the incipient bond ($\nu_i = 377.7$ and -392.6 cm^{-1} for *ax*-TS and *eq*-TS, respectively). The incipient bond distances for $LiAlH_4$ transition states were 1.531 and 1.556 Å for *ax*- and *eq*-TS, respectively, which are far shorter than the unrealistically long incipient bonds of LiH transition states [2.739 (*ax*-TS) and 2.510 (*eq*-TS) Å; B3LYP/6-31+G(d)]. In contrast to the LiH cases, the relative earliness of *ax*- and *eq*-TS with $LiAlH_4$ in terms of the incipient bond length suggests that the latter is moderately earlier than the former. Such a trend is also seen in the bond lengths of other parts of the structures, such as the C=O, Al–H and O–Li bond distances. Thus the incipient bond for *ax*-TS may be stronger than that for *eq*-TS. The hydride approaching angles in the $LiAlH_4$ transition structures [109.8 (*ax*-TS) and 109.5° (*eq*-TS)] are greater by ~ 20° than those for the LiH cases [85.6 (*ax*-TS) and 90.3° (*eq*-TS)] The former values are similar to the average angle of nucleophile approach (107°) observed by crystallographic investigation of some crystalline ketones.[5] The torsion angles of the cyclohexanone moiety along C2–C1–C6–C5 are 44.2 and 63.8° for *ax*- and *eq*-TS, respectively. The latter is much more distorted than the LiH transition states [42.5 (*ax*-TS) and 56.5° (*eq*-TS)]. The magnitude of the torsional strain of the cyclohexanone moieties of $LiAlH_4$ transition states relative to ground-state cyclohexanone optimized at the B3LYP/6-31+G(d) level was 11.9 and 10.9 kcal mol^{-1} for *ax*-TS and *eq*-TS, respectively [single point calculation at the MP2/6-31+G(d) level]. As such, *ax*-TS is slightly (1.0 kcal mol^{-1}) more distorted than *eq*-TS, in sharp contrast to the LiH case previously reported.[6] It is therefore concluded that the torsional strain is not responsible for π-facial stereoselectivity in cyclohexanone reduction as pointed out previously by Frenking using the LiH transition states.[7]

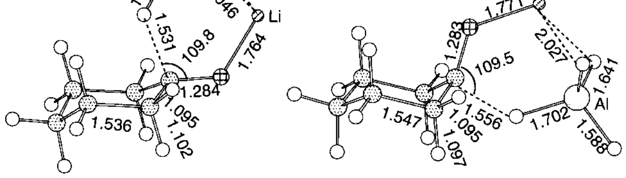

Fig. 1 Selected structural parameters for the transition states of cyclohexanone reduction with $LiAlH_4$ obtained at the B3LYP/6-31+G(d) level. Bond lengths are in Å and angles are in degrees. *E* indicates the total electronic energy.

It is expected that the magnitude of the AP effects may be initially significant, but should gradually be diminished along the IRC toward the transition state for the following two reasons. First, as the reaction proceeds, the strength of the incipient bond increases, causing some energy increase in the antibonding ($\sigma^{‡*}$) level of the incipient bond accompanied by energy reduction of its bonding ($\sigma^{‡}$) level. This may cause reduction of both (Cieplak and Felkin–Anh) antiperiplanar stabilization mechanisms involving the incipient bond. Secondly, as the reaction proceeds, hybridization of the carbonyl carbon (C1) changes from sp^2 to sp^3, and therefore the length of the intervening σ_{C1-C2} bond increases to cause inevitable reduction in the magnitude of the antiperiplanar hyperconjugation toward transition state. Consequently it is expected that antiperiplanar hyperconjugation mechanisms may operate effectively in the early stages and that the difference in the magnitude between the two π-faces of the carbonyl plane may be reduced steadily along the reaction coordinate toward the transition state, where it may vanish completely.

To evaluate the relative magnitude of the AP effects in the $LiAlH_4$ transition states, a natural bond orbital (NBO) program[4] combined with intrinsic reaction coordinate (IRC) calculations with GAUSSIAN 94[8] were applied at the B3LYP/6-31+G(d) level. IRC calculation clearly showed that the above structures with negative frequencies (Fig. 1) were indeed the transition states. As shown in Fig. 2, structural analysis of the reaction along the IRC indicated a steady decrease in the AP effects towards the transition states. The percentage elongation of the vicinal antiperiplanar bonds (relative to the corresponding bonds of ground-state cyclohexanone optimized at the same level) in *eq*-TS (0.33–0.14%) is always greater than that in *ax*-TS (0.13–0.05%) along the reaction coordinate. It should be noted here that elongation of the antiperiplanar bonds is reduced to almost zero (0.05%) in *ax*-TS (IRC = 0) in agreement with the above prediction. The relative magnitude of the transition state AP effects (*ax*-TS vs. *eq*-TS) as well as the marginal AP effect in *ax*-TS clearly indicate that if the AP effects were the

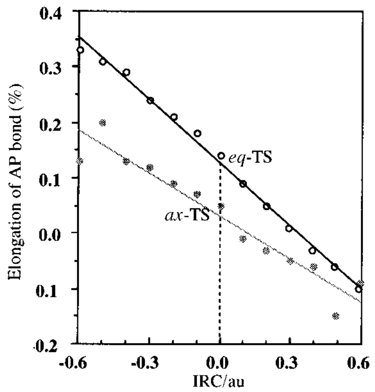

Fig. 2 Elongation of vicinal antiperiplanar bonds along the IRC for cyclohexanone reduction with $LiAlH_4$ [B3LYP/6-31+G(d)].

major mechanism of facial stereoselection in cyclohexanone reduction, stereoselectivity opposite to the experimental result must be observed, contrary to the predictions of both conventional models.[1,3]

In agreement with the above theoretical outcomes, NBO analysis along the IRC toward the transition states suggested that a small amount of electronic charge was removed from the vicinal antiperiplanar bonds all the way along the transition states [0.015–0.008 electrons for the *eq*-attack and 0.011–0.005 electrons for the *ax*-attack based on the bond population for the corresponding antiperiplanar bonds of cyclohexanone optimized at the B3LYP/6-31+G(d) level] and that they monotonously decreased along IRC as shown in Fig. 3. The small reduction in the amount of electrons in the antiperiplanar bonds clearly indicated that the Cieplak hyperconjugation effect should be greater than the Felkin–Anh hyperconjugation effect. The electron population of the incipient bond ($\sigma^\ddagger$) determined with natural resonance theoretical (NRT) analysis[4] was 0.696 and 0.663 for *ax*- and *eq*-TS, respectively. These values strongly suggest significantly electron-deficient incipient bonds in the transition states for cyclohexanone reduction in agreement with Cieplak's proposal.[1] Thus the greater AP effect at *eq*-TS compared with *ax*-TS as indicated by the percentage elongation of the antiperiplanar bonds (*ax*-TS = 0.05% and *eq*-TS = 0.14%) as well as by the magnitude of electron transfer (*ax*-TS = 0.005 *e* and *eq*-TS = 0.008 *e*) strongly suggests that the AP effect may not be an essential mechanism of π-facial stereoselection.

It was found that within the framework of modern molecular orbital methods operational direction of the AP effect involving an incipient bond is not necessarily consistent with a preferred direction of hydride attack, as seen in the following transition state examples of $LiAlH_4$ reduction obtained at the B3LYP/6-31+G(d) level. The 3,5-dithiacyclohexanone reduction with $LiAlH_4$, the *eq*-attack of which is preferred to the *ax*-attack,[9] shows unusual behavior of the AP effect: the C2–S3 bond in *eq*-TS is shortened (−0.11%), while the C2–H*ax* bond in *ax*-TS is elongated (+0.25%) relative to the starting ketone. The reduction in the NBO[5] electron population in the antiperiplanar bonds at C2 and C6 (−0.012 and 0.000 for *ax*- and *eq*-TS, respectively) was also consistent with this interesting trend. It is clear that the experimental stereochemistry cannot be explained in terms of the AP effect. Apparently the AP effect is more significant in *ax*-TS, although *ax*-TS is less stable by 1.39 kcal mol^{-1} than *eq*-TS.

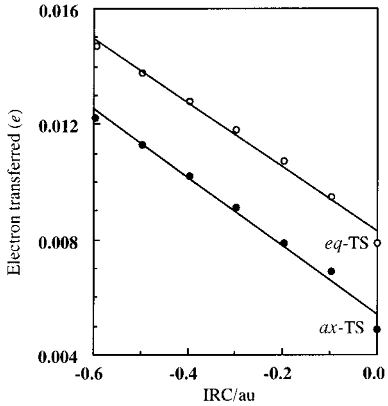

Fig. 3 Plot of the electron population moved from an antiperiplanar bond against the IRC for cyclohexanone reduction with $LiAlH_4$ [B3LYP/6-31+G(d)].

Another intriguing case is the adamantanone system. It has long been known that adamantanone is less reactive in hydride reduction than cyclohexanone,[10] despite the theoretical observation that the AP effects are much greater in adamantanone than in cyclohexanone. The $LiAlH_4$ transition state of the parent adamantan-2-one shows more than twice (+0.34% elongation of the C–C bond) as large AP effects as those of cyclohexanone (+0.05 and +0.14% for *ax*- and *eq*-TS, respectively). While 5-methyladamantan-2-one shows only a marginal difference in percentage elongation of the vicinal antiperiplanar C–C bond between the *syn*- (+0.40%) and *anti*-TS (+0.38%) (relative to the ground-state 5-methyladamantan-2-one), 5-fluoroadamantan-2-one, which gives preferential *syn*-attack in $NaBH_4$ reduction (63 : 37),[11] shows a larger AP effect in *anti*-TS (+0.48%) than in *syn*-TS (+0.39%) relative to the ground-state 5-fluoroadamantan-2-one. In both of these cases, the *syn*-TS is more stable than the *anti*-TS by 0.12 (5-methyladamantan-2-one) and 0.23 (5-fluoroadamantan-2-one) kcal mol^{-1}. Another case which shows similar behavior is 5-azaadamantan-2-one *N*-oxide, which prefers 96% *syn*-attack upon reduction with $NaBH_4$.[12] The $LiAlH_4$ reduction transition states of this compound show elongation of the vicinal antiperiplanar bonds of +1.00% (*anti*-TS) and +0.95% (*syn*-TS) relative to the parent ketone. Virtually no difference in the magnitude of the AP effects over two carbonyl faces is evident.

The present analysis strongly suggests that the transition state effects are most likely to have minor effects on facial selection. This 'unusual' behavior may be readily understood if one considers the mechanism (the direction of the force vector on hydride nucleus) of the AP effect which operates against the incipient bond formation: the effect causes elongation of the incipient bond against the force vector on hydride directed toward bond formation with the carbonyl. We emphasize again that the difference in the magnitude of the driving force of the reaction generated over the two π-faces of the carbonyl plane through orbital interactions[13] between ketone and hydride should be the origin of π-facial stereoselectivity in cyclohexanone reduction.[14]

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